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Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-β-Phosphorylated Enamides: Highly Enantioselective Access to β-Aminophosphines

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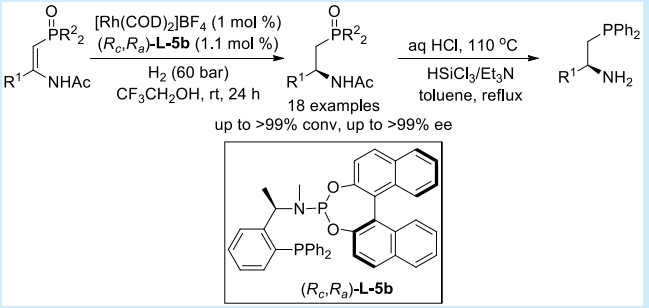
Supporting Information

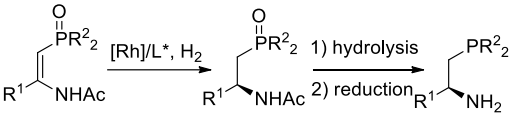
ABSTRACT: A catalytic asymmetric hydrogenation of β-phosphorylated enamides for enantioselective access to optically active β-aminophosphine derivatives is reported. Critical to the success of this method was the employment of rhodium catalysis in concert with an unsymmetrical hybrid chiral phosphine-phosphoramidite ligand. A wide range of aromatic β-phosphorylated enamides could be hydrogenated in full conversion and with perfect enantioselectivity even at low catalyst loadings (S/C = 1000). β-Aminophosphine oxides could be readily hydrolyzed and reduced, thus providing an efficient route to catalytically important chiral β-aminophosphines.



Optically active β-aminophosphine derivatives have been well established as chiral scaffolds for the construction of a diversity of ligands or organocatalysts, thus playing an important role in the areas of asymmetric catalysis and coordination chemistry.[1] β-Aminophosphines are typically prepared using enantiopure starting materials (mostly natural or unnatural amino acids) and chiral auxiliaries or by resolution of the racemic aminophosphines.[1a] In contrast, catalytic asymmetric synthesis of chiral β-aminophosphines remains elusive, all focusing on the metal-catalyzed or organocatalytic phospha-Michael addition of diarylphosphines to nitroalkenes following a nitro group reduction step.[2] As the reported catalytic systems mostly suffered from the relatively narrow substrate scope, high catalyst loading, or insufficient enantioselectivity, the development of new catalytic protocols for highly efficient and enantioselective synthesis of structurally diverse chiral β-aminophosphine derivatives is therefore highly desirable and remains a challenge.

Over the past decade, our laboratory has reported an array of structurally diverse aminophosphines and demonstrated their importance in asymmetric catalysis.[3] In keeping with our long-standing goal in the construction of the structural diversity of chiral aminophosphine skeletons for asymmetric catalysis, we sought to develop a general method for catalytic asymmetric synthesis of optically active β-aminophosphines. For its inherent efficiency and atom economy,[4] catalytic asymmetric hydrogenation of β-phosphorylated enamides should be one of the most direct and convenient alternatives to chiral β-aminophosphine derivatives. Unexpectedly, there is no example that details the success to date, although catalytic asymmetric hydrogenation of various β-functionalized enamides including ester,[5] sulfone,[6] nitrate,[7] phosphonate,[8] and sulfide[9] has been extensively studied, highlighting the challenging nature of this substrate class. By the employment of the Rh-catalysis in combination with a chiral 1-phenylethylamine-derived phosphine-phosphoramidite ligand developed within our group, herein we report the first catalytic asymmetric hydrogenation of β-phosphorylated enamides, affording various chiral β-aminophosphine oxides in full conversions and with up to >99% ee even at low catalyst loading of 0.1 mol %. In particular, chiral β-aminophosphine oxides could be readily converted into optically active β-aminophosphines by the hydrolysis and reduction, thus providing a facile and efficient access to structurally diverse chiral β-aminophosphines (Scheme 1).

Scheme 1. Strategy for Asymmetric Synthesis of Chiral β-Aminophosphines via Rh-Catalyzed Hydrogenation



β-Phosphorylated enamides could be readily prepared via $Mn(acac)_3$-mediated oxidative coupling of enamides with phosphine oxide as reported by Zhang and Xiong recently, and only (*Z*)-isomers were obtained as the products.[10] Initially, Rh-catalyzed asymmetric hydrogenation of (*Z*)-*N*-(2-(diphenylphosphoryl)-1-phenylvinyl)acetamide **1a** was chosen as the model reaction to optimize the reaction conditions. The

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reaction was conducted in CH_2Cl_2 under an H_2 pressure of 50 bar at room temperature for 24 h in the presence of 1 mol % of $[Rh(COD)_2]BF_4$, evaluating a variety of chiral phosphorus ligands available from commercial sources or developed within our group (Figure 1). As shown in Table 1, commercially

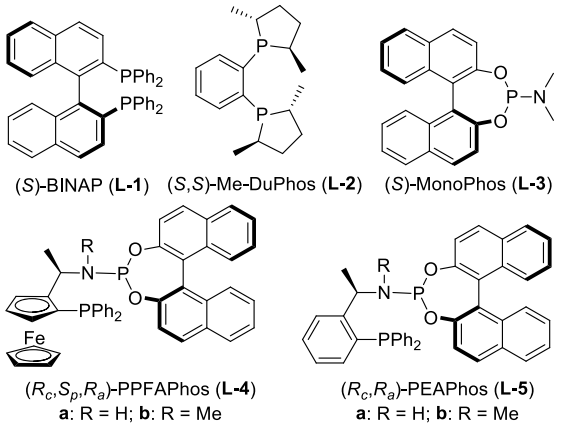
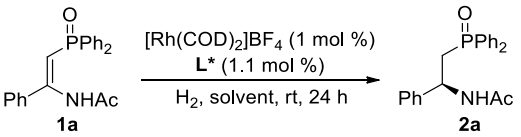


Figure 1. Ligands for Hydrogenation.

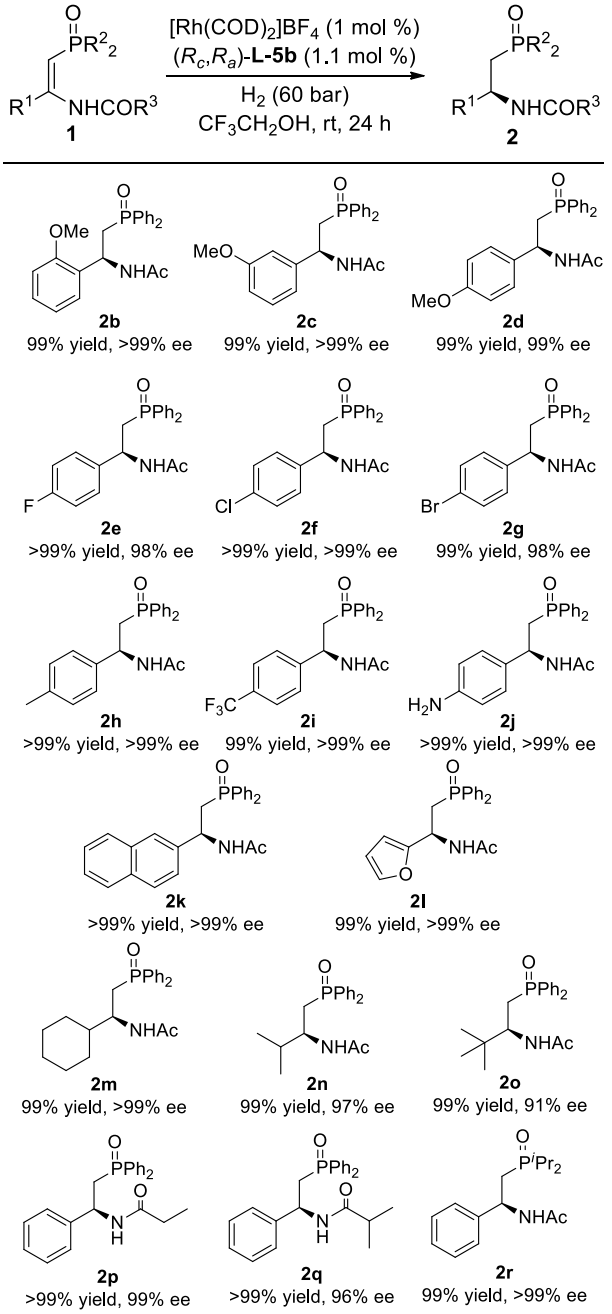
Table 1. Optimization Studies on Rh-Catalyzed Asymmetric Hydrogenation of (Z)-*N*-(2-(Diphenylphosphoryl)-1-phenylvinyl)acetamide 1a[a]



entry	ligand	solvent	H_2 (bar)	conv[b] (%)	ee[c] (%)
1	**L-1**	CH_2Cl_2	50	<10	–
2	**L-2**	CH_2Cl_2	50	95	52
3[d]	**L-3**	CH_2Cl_2	50	<10	–
4	**L-4a**	CH_2Cl_2	50	85	73
5	**L-4b**	CH_2Cl_2	50	98	92
6	**L-5a**	CH_2Cl_2	50	90	97
7	**L-5b**	CH_2Cl_2	50	99	>99
8	**L-5b**	CH_2Cl_2	60	>99	>99
9	**L-5b**	MeOH	60	99	88
10	**L-5b**	PhMe	60	<10	–
11	**L-5b**	THF	60	<10	–
12	**L-5b**	TFE	60	>99	98
13[e]	**L-5b**	TFE	60	>99	>99
14[e]	**L-5b**	CH_2Cl_2	60	<10	–
15[f]	**L-5b**	TFE	60	>99	93

[a]Unless otherwise noted, all reactions were carried out with a Rh/ligand/**1a** (0.125 mmol) ratio of 1:1.1:100 in 2.5 mL of solvent at room temperature under H_2 for 24 h. [b]Conversion was determined by GC. [c]Ee was determined by HPLC analysis using a chiral stationary phase. [d]Rh/**L-3** = 1:2. [e]S/C = 200. [f]S/C = 1000. COD = 1,5-cyclooctadiene, TFE = CF_3CH_2OH.

Scheme 2. Scope Study for the Rh-Catalyzed Asymmetric Hydrogenation of (Z)-β-Phosphorylated Enamides 1[a]



[a]All reactions were carried out with a $[Rh(COD)_2]BF_4$/(R_c,R_a)-**L-5b**/**1** (0.125 mmol) ratio of 1:1.1:100 in 2.5 mL of CF_3CH_2OH at room temperature under a H_2 pressure of 60 bar for 24 h, except S/C = 10/1 for **1o**. Full conversions were achieved in all cases. Isolated yields were provided in all cases. Ee was determined by HPLC analysis using a chiral stationary phase.

available BINAP (**L-1**) and MonoPhos (**L-3**) exhibited poor activity toward this hydrogenation (entries 1 and 3), while DuPhos (**L-2**) displayed good activity but moderate enantioselectivity (entry 2).

To our delight, unsymmetrical hybrid chiral phosphine-phosphoramidite ligands developed within our group were found to be a suitable ligand class for the hydrogenation with chiral 1-phenylethylamine-derived phosphine-phosphoramidite ligand (R_c,R_a)-PEAPhos **L-5b** as the optimized one (entries 4–7). Promoting H_2 pressure to 60 bar led to the hydrogenation in full conversion and >99% ee (entry 8). The nature of the solvent dramatically affected the hydrogenation (entries 8–12). Thus, very low conversions were observed in toluene and THF, while good catalytic performance was achieved in MeOH, CH_2Cl_2, and trifluoroethanol (TFE). TFE proved to be the best solvent, as the perfect catalytic performance was

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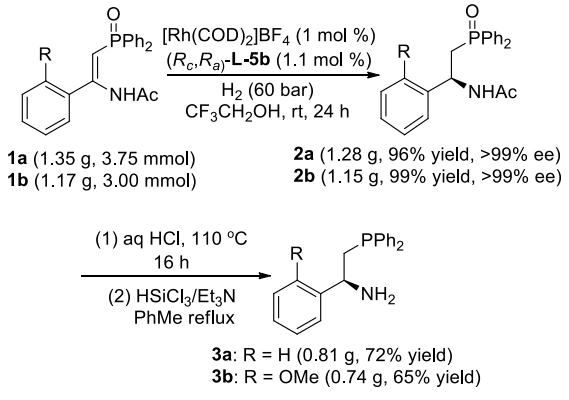
maintained even by lowering the catalyst loading to 0.5 mol % (entry 13). In this case, the hydrogenation in CH_2Cl_2 only showed low conversion (entry 14). The high efficiency of the present catalytic system was further demonstrated by performing the hydrogenation at a catalyst loading as low as 0.1 mol %, in which full conversion with 93% ee was achieved (entry 15). The absolute stereochemistry of the resulting β-aminophosphine oxide **2a** was determined to be *S* by the comparison of the optical rotation with the reported value in the literature[11] after the derivation to the corresponding 2-(diphenylphosphino)-1-phenylethanamine.

Under the optimized conditions, the scope of (*Z*)-β-phosphorylated enamides **1** was examined, and the results are summarized in Scheme 2. Initially, various 1-phenyl substituted enamides **1b**−**j** were submitted to the hydrogenation. Both electron-donating and -withdrawing substituents were well tolerated, regardless of the position (*ortho*-, *meta*-, or *para*-position) of the phenyl ring. In all cases, the hydrogenation led to the corresponding β-aminophosphine oxides **2b**−**j** in full conversions and with perfect enantioselectivities (98 → 99% ee). 2-Naphthyl substrate **1k** was hydrogenated smoothly to give the desired product **2k** in full conversion and >99% ee. Heteroaromatic enamide **1l** worked well in the hydrogenation, resulting in the hydrogenation product **2l** in full conversion and with >99% ee. Of note, aliphatic enamides **1m**−**o** were also well tolerated and could be hydrogenated in full conversion and with high to perfect enantioselectivities. We also investigated the effect of the *N*-acyl group in the hydrogenation, and the results indicated the hydrogenation of all enamides **1p**−**q** with different acyl groups led to excellent outcomes although the increased steric hindrance of acyl group slightly decreased the enantioselectivity. An alkyl substituent at the P-atom was also well tolerated, giving the hydrogenation product **2r** in full conversion and with >99% ee.

To explore the synthetic potential of this Rh-catalyzed hydrogenation, two gram-scale experiments were performed with **1a** and **1b** under the standard conditions. The hydrogenations proceeded smoothly and gave the desired products (*S*)-**2a** and (*S*)-**2b** in high isolated yields and with perfect enantioselectivity (Scheme 3). The acetyl group of (*S*)-**2a** or **2b** was readily removed in aq HCl to afford the corresponding β-aminophosphine oxide. The reduction of β-aminophosphine oxides with $HSiCl_3/Et_3N$ in toluene led to catalytically important β-aminophosphine (*S*)-**3a** and **3b** in 72% and 65% yield, respectively.

Scheme 3. Gram-Scale Experiments and Synthetic Application



In conclusion, we have developed an efficient approach for asymmetric hydrogenation of (*Z*)-β-phosphorylated enamides to generate optically active β-aminophosphine derivatives. Using a combination of $[Rh(COD)_2]BF_4$ with an unsymmetrical hybrid phosphine-phosphoramidite ligand as the catalyst, a series of (*Z*)-β-phosphorylated enamides could be hydrogenated smoothly to provide the desired β-aminophosphine oxides in in full conversions and with perfect enantioselectivity (up to >99% ee) even at low catalyst loadings (S/C = 1000). Furthermore, β-aminophosphine oxides could be readily hydrolyzed and reduced, thus providing an effective and concise route to catalytically important and structurally diverse chiral β-aminophosphines. Further investigations on the application of chiral β-aminophosphines in asymmetric hydrogenation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03174.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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